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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,826	04/16/2004	Victor Gurewich	15702-004001	1731

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,826	GUREWICH ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *7-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/28/04, 4/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *PTO-1449 of 6/22/05*.

DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-6, in the reply filed on August 26, 2005 is acknowledged. Claims 7-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. No claims have been amended, added or canceled. Accordingly, claims 1-6 are examined on the merits herewith.

Applicants' argument in response to the restriction requirement has been considered, but it is not persuasive. Applicants assert that Groups I-III should be examined together because, in each case, the same composition is administered. Applicants cite from the MPEP that inventions are unrelated if it can be shown that they are not used together and that they have different modes of operation, different functions or different effects. Applicants assert that the M5 protein in each group has the same mode of operation and causes the same effect in each method.

In reply, each of Groups I-III is drawn to method of treating a patient with a different disease. These are not composition claims, i.e., drawn to compositions comprising the M5 protein. Thus, the patient on whom the method is carried out is different in each group. Because the different groups are methods of treating different patient populations (stroke patients, heart attack patients, surgery patients), the different inventions are not used together. Additionally, treating stroke patients is different than treating heart attack patients and surgery patients. Thus, the different methods have

different functions. The different methods also have different modes of operation, because, in treating stroke patients, the drug must be administered in a form that will cross the blood-brain barrier at an effective dosage. Intravenous administration is therefore the most likely form of giving the drug. In surgery patients, local administration would be preferable, and in heart attack patients, particularly if they are not hospitalized, oral administration would be preferable. In view of the foregoing, the restriction requirement is maintained and is made final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Liu et al. (US 5,472,692) in view of Brearley et al. (US 2002/0098179) and Pinsky (US 2002/0138858).

Liu discloses a mutant pro-urokinase (pro-UK) that is used and administered as a thrombolytic agent in the same way as pro-urokinase and urokinase. The mutant pro-UK is injected as a bolus of 20-60 mg or administered intravenously at a rate of 40-200 mg/hour (see col. 16, lines 14-25). The mutant is a flexible loop mutant and comprises the mutation Lys^{300} to His^{300} (see col. 2, lines 27-35). Liu et al. also disclose that mutant pro-UK is a superior drug compared to UK or pro-UK because it interacts with specifically with plasminogen so that occlusions in blood vessels are dissolved with comparatively reduced side effects. There is less bleeding and less degradation of fibrin, fibrinogen, platelets and blood vessel walls. The undesired activity (fibrinogenolysis and plasminogen activation) is about 10-fold less in mutant pro-UK compared to pro-UK (see col. 1, line 7, to col. 2, line 18). Liu et al. do not specifically discloses administering the pro-UK mutant to a person who has had a stroke.

Brearley et al. disclose that pro-UK is a thrombolytic agent that is administered to stroke patients following the stroke and that this agent has the same activity as t-PA. Pro-UK or t-PA should be given within three hours of the onset of symptoms to minimize damage to the brain tissue in the area of the thrombus due to lack of oxygen and glucose. Pro-UK is likely to have the same restricted use as t-PA, which is that it should be administered only to patients who have had an ischemic stroke (occluded cerebral blood vessel) and not to patients who have had a haemorrhagic stroke (ruptured cerebral blood vessel). Following the stroke, and before t-PA or pro-UK may be

administered, a patient must be diagnosed by CT scan to determine the type of stroke (medical confirmation). If the stroke was haemorrhagic, t-PA or pro-UK may not be administered, as these exacerbate bleeding (see p. 2, paragraph 9). Thus, it would have been obvious to one of ordinary skill in the art at the time that the invention was made that if the medical confirmation of type of stroke indicated that the patient had not had a haemorrhagic stroke, an ischemic stroke, or blood vessel occlusion, would have been confirmed and an effective amount of pro-UK, such as 40-200 mg/hour, as disclosed by Liu et al., would have been administered. Further, it would have been obvious to one of ordinary skill in the art to use a mutant pro-UK, as disclosed by Liu et al., to treat a stroke patient, because Liu et al. disclose that mutant pro-UK has greatly reduced side effects.

Pinsky also discloses that recombinant pro-UK may be used to treat ischemic stroke, but that the therapeutic utility is limited due to the risk of intracranial haemorrhage. It is important to identify novel strategies of reducing intravascular thrombosis without increasing the risk of intracerebral haemorrhage (see p. 1, paragraph 3). The strategy of Pinsky is to identify agents that inhibit platelet aggregation or fibrin deposition in ischemic tissue to treat stroke victims. But, it would have been obvious to one of ordinary skill in the art to pursue other strategies, such as using a form of a drug for treating stroke that has a greatly reduced risk of causing bleeding, such as the mutant pro-UK of Liu.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al.

(US 5,472,692) in view of Brearley et al. (US 2002/0098179) and Pinsky (US 2002/0138858) and further in view of Barnwell et al. ("Safety and efficacy of delayed intraarterial urokinase therapy with mechanical clot disruption for thromboembolic stroke," Am J Neuroradiology, 15(10):1817-1822, 1994) and Parsons et al. ("Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke," Ann Neurol 51(1):28-37, 2001). The teachings of Liu et al., Brearley et al. and Pinsky are discussed above. These references do not disclose administering mutant pro-UK or pro-UK more than three hours after the onset of stroke symptoms.

Parsons et al., however, disclose administration of the recombinant thrombolytic drug t-PA to stroke patients up to six hours following an ischemic stroke. These patients' brains were examined by two imaging techniques, diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). It was found that if there was a mismatch in the patterns produced by the different techniques in a patient, the patient had a penumbra of hypoperfused, but salvageable, tissue in the area of the lesion. In such patients, treatment with the thrombolytic drug produced improvement in recanalization and reperfusion in the affected area and stroke outcome (see pp. 28 and 34). It would have been obvious to one of ordinary skill in the art to administer the mutant pro-UK drug of Liu et al. to a patient more than three hours after the onset of stroke symptoms, because Parsons et al. teach that, if the patient is found to have a PWI/DWI imaging mismatch, the patient benefits from the drug because there is partial recovery of the tissue in the area of the stroke lesion. The recovery of the penumbral tissue is due to the thrombolytic activity of the drug. Thus, one of ordinary skill in the art would have

recognized that a drug with thrombolytic activity may be administered 3-6 hours following the onset of stroke symptoms; the drug need not be t-PA. Another drug with the desired thrombolytic properties that does not cause excessive bleeding, such as the mutant pro-UK of Liu et al. would be expected to work.

Similarly, Barnwell et al. disclose administration of urokinase to stroke patients 3.5 to 48 hours after the onset of symptoms (see p. 1818). Significant improvement in neurologic and functional outcomes were noted in nine out of 13 patients. Ten patients had successful vessel recanalization (see Abstract and Table on p. 1819). It would have been obvious to one of ordinary skill in the art to administer the mutant pro-UK drug of Liu et al. to a patient more than three hours after the onset of stroke symptoms, because Barnwell et al. teach that administration of urokinase more than three hours after the onset of stroke symptoms is effective in most cases if delivered to the area of the lesion. The improvements in the patients are due to the thrombolytic activity of the drug. Thus, one of ordinary skill in the art would have recognized that an improved urokinase, such as the mutant pro-UK of Liu et al., may be administered with efficacy more than three hours following the onset of stroke symptoms. A urokinase with the desired thrombolytic properties that does not cause excessive bleeding and that does not dissolve haemostatic, sealing fibrin clots in blood vessels, such as the mutant pro-UK of Liu et al., would be expected to work at least as well as the urokinase of Barnwell et al.

In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1653

rk/2005-09-14